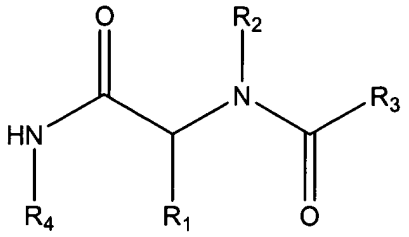
CLAIMS

What is claimed is:

1. A method of inhibiting rejection of a transplanted organ, tissue or cell in a mammal, the method comprising the step of administering to the recipient mammal an effective amount of an immunosuppressive agent and an effective amount of a compound represented by the following structural formula:



or a physiological salt thereof, wherein:

R_1 is a substituted or unsubstituted aryl group or a substituted or unsubstituted alkyl group;

R_2 is an optionally substituted aralkyl group or an alkyl group substituted with $-NR_5R_6$;

R_3 is a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group;

R_4 a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group; and

R_5 and R_6 are independently selected from a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group or R_5 and R_6 taken together with the nitrogen to which they are attached are a non-aromatic heterocyclic group.

2. The method of Claim 1 wherein the transplanted organ, tissue or cell is a transplanted heart, kidney, lung, liver, pancreas, skin or bone marrow.

3. The method of Claim 1 wherein the mammal is the recipient of a transplanted stem cell(s).

4. The method of Claim 1 wherein the transplanted organ, tissue or cell is xenogenic or bio-engineered.

5. The method of Claim 1 wherein the immunosuppressive agent is an anti lymphocyte antibody.

6. The method of Claim 1 wherein the immunosuppressive agent is an anti-CD40L monoclonal antibody or rapamycin.

7. The method of Claim 1 wherein R_2 is an optionally substituted heteroaralkyl group or an alkyl group substituted with $-NR_5R_6$.

8. The method of Claim 7 wherein:

a) R_1 is an optionally substituted aryl group or an optionally substituted C_1-C_4 aralkyl group;

b) R_3 is an optionally substituted aryl group or an optionally substituted C_1-C_4 aralkyl group; and

c) R_4 is an optionally substituted aryl group, an optionally substituted cycloalkyl group, an optionally substituted C_1-C_4 aralkyl group or an optionally substituted C_1-C_4 cycloalkylalkyl group.

9. The method of Claim 7 wherein:

a) R_1 is an optionally substituted phenyl group or an optionally substituted phenyl-C_1-C_4 alkyl group;

b) R_3 a substituted or unsubstituted phenyl, phenyl-C_1-C_4-alkyl, diphenyl-C_1-C_4-alkyl, pyrazolyl, pyrazolyl-C_1-C_4-alkyl, indolyl, indolyl-C_1-C_4-alkyl, thienylphenyl, thienylphenyl-C_1-C_4-alkyl, furanylphenyl, furanylphenyl-C_1-C_4-alkyl, fluorenyl, fluorenyl-C_1-C_4-alkyl, naphthyl, naphthyl-C_1-C_4-alkyl, quinoxalinyl, quinoxalinyl-C_1-C_4-alkyl, an optionally substituted quinazolinyl, an optionally substituted quinazolinyl-C_1-C_4-alkyl, pyrolyl, pyrolyl-C_1-C_4-alkyl, thienyl, thienyl-C_1-C_4-alkyl, furanyl or furanyl-C_1-C_4-alkyl; and

c) R_4 is an optionally substituted phenyl group, an optionally substituted phenyl-C_1-C_4-alkyl group, an optionally substituted diphenyl-C_1-C_4-alkyl group, an optionally substituted C_3-C_8-cycloalkyl-C_1-C_4-alkyl group or an optionally substituted di-(C_3-C_8-cycloalkyl)-C_1-C_4-alkyl group.

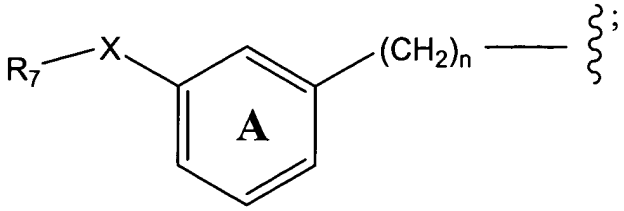
10. The method of Claim 9 wherein R_2 is an optionally substituted imadazolyl-C_1-C_4-alkyl group or a C_1-C_4 alkyl group substituted with $-NR_5R_6$.

11. The method of Claim 10 wherein:

R_1 is a phenyl group or phenyl-C_1-C_4 alkyl group each optionally substituted with R, $-CH_2R$, $-OCH_2R$, $-CH_2OC(O)R$, -OH, halogen, -OR, -O-COR, -COR, -CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$, -NHR, $-N(R)_2$, -COOR, -CHO, $-CONH_2$, -CONHR, $-CON(R)_2$, -NHCOR, -NRCOR, $-NHCONH_2$, -NHCONRH, $-NHCON(R)_2$, $-NRCONH_2$, -NRCONRH, $-NRCON(R)_2$, $-C(=NH)-NH_2$, -C(=NH)-NHR, $-C(=NH)-N(R)_2$, $-C(=NR)-NH_2$, -C(=NR)-NHR, $-C(=NR)-N(R)_2$, $-NH-C(=NH)-NH_2$, -NH-C(=NH)-NHR, $-NH-C(=NH)-N(R)_2$,

-NH-C(=NR)-NH_2, -NH-C(=NR)-NHR, -NH-C(=NR)-$N(R)_2$, -NRH-C(=NH)-NH_2, -NR-C(=NH)-NHR, -NR-C(=NH)-$N(R)_2$, -NR-C(=NR)-NH_2, -NR-C(=NR)-NHR, -NR-C(=NR)-$N(R)_2$, $-SO_2NH_2$, $-SO_2NHR$, $-SO_2N(R)_2$, -SH or -SokR;

R_3 is represented by the following structural formula:



R_4 is 2,2-diphenylethyl, 2-phenylethyl, benzyl, diphenylmethyl, 1,2-diphenylethyl, 3,3-diphenylpropyl, benzyl, or 2-pyridylethyl, each optionally substituted with -OH, halogen, R, $-CH_2R$, $-OCH_2R$, $-CH_2OC(O)R$, -OR, -O-COR, -COR, -CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$, -NHR, $-N(R)_2$, -COOR, -CHO, $-CONH_2$, -CONHR, $-CON(R)_2$, -NHCOR, -NRCOR, $-NHCONH_2$, -NHCONRH, $-NHCON(R)_2$, $-NRCONH_2$, -NRCONRH, $-NRCON(R)_2$, -C(=NH)-NH_2, -C(=NH)-NHR, -C(=NH)-$N(R)_2$, -C(=NR)-NH_2, -C(=NR)-NHR, -C(=NR)-$N(R)_2$, -NH-C(=NH)-NH_2, -NH-C(=NH)-NHR, -NH-C(=NH)-$N(R)_2$, -NH-C(=NR)-NH_2, -NH-C(=NR)-NHR, -NH-C(=NR)-$N(R)_2$, -NRH-C(=NH)-NH_2, -NR-C(=NH)-NHR, -NR-C(=NH)-$N(R)_2$, -NR-C(=NR)-NH_2, -NR-C(=NR)-NHR, -NR-C(=NR)-$N(R)_2$, $-SO_2NH_2$, $-SO_2NHR$, $-SO_2N(R)_2$, -SH or $-SO_kR$;

Ring **A** substituted or unsubstituted; R_7 is an optionally substituted phenyl, furanyl, thienyl or pyridyl group; n is an integer from 1-4; and X is a bond, CH_2, OCH_2, $CH_2OC(O)$, CO, OC(O), C(O)O, O, S, SO or SO_2;

each R is independently C_1-C_4 alkyl or phenyl optionally substituted with amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl,

alkylaminocarbonyl, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl; and

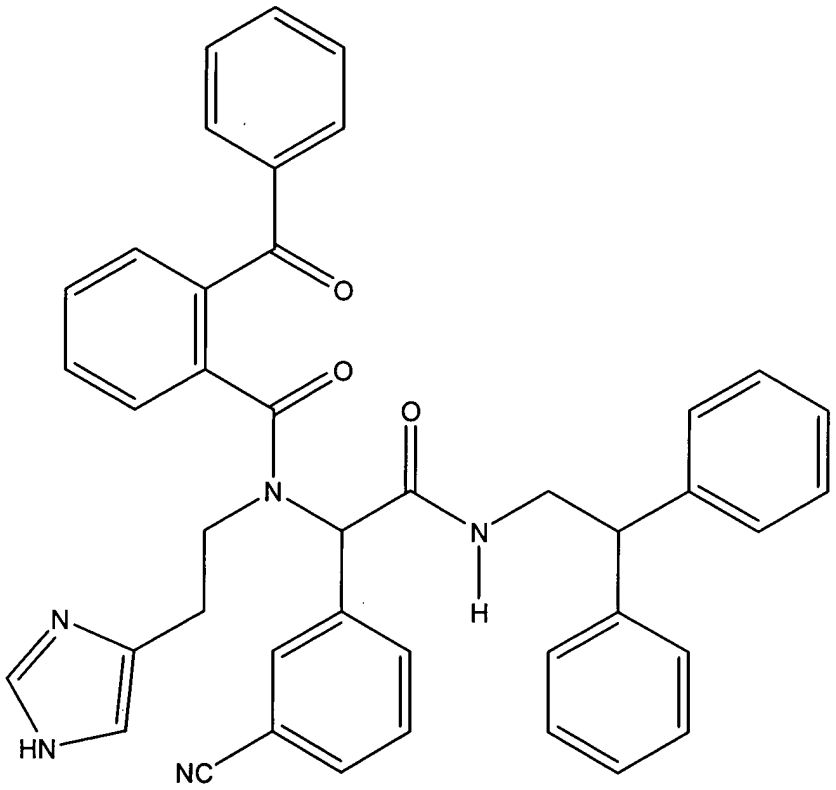
k is zero, one or two.

12. The method of Claim 11 wherein R_1 is a phenyl group or phenyl-C_1-C_2 alkyl group, each optionally substituted with C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, CN, C_1-C_4-alkylthiol, C_1-C_4-haloalkyl or phenoxy; R_4 is 2,2-diphenylethyl, 2-phenylethyl, benzyl, diphenylmethyl, 1,2-diphenylethyl, 3,3-diphenylpropyl, benzyl, or 2-pyridylethyl, each optionally substituted with C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, CN, C_1-C_4-alkylthiol, C_1-C_4-haloalkyl or phenoxy; R_7 is an optionally substituted phenyl group; n is 1; and X is CO.

13. The method of Claim 12 wherein Ring **A** is unsubstituted and R_7 is a phenyl group optionally substituted with R, -CH_2R, -OCH_2R, -$CH_2OC(O)$R, -OH, halogen, -OR, -O-COR, -COR, -CN, -NO_2, -COOH, -SO_3H, -NH_2, -NHR, -$N(R)_2$, -COOR, -CHO, -$CONH_2$, -CONHR, -$CON(R)_2$, -NHCOR, -NRCOR, -$NHCONH_2$, -NHCONRH, -$NHCON(R)_2$, -$NRCONH_2$, -NRCONRH, -$NRCON(R)_2$, -$C(=NH)$-NH_2, -$C(=NH)$-NHR, -$C(=NH)$-$N(R)_2$, -$C(=NR)$-NH_2, -$C(=NR)$-NHR, -$C(=NR)$-$N(R)_2$, -NH-$C(=NH)$-NH_2, -NH-$C(=NH)$-NHR, -NH-$C(=NH)$-$N(R)_2$, -NH-$C(=NR)$-NH_2, -NH-$C(=NR)$-NHR, -NH-$C(=NR)$-$N(R)_2$, -NRH-$C(=NH)$-NH_2, -NR-$C(=NH)$-NHR, -NR-$C(=NH)$-$N(R)_2$, -NR-$C(=NR)$-NH_2, -NR-$C(=NR)$-NHR, -NR-$C(=NR)$-$N(R)_2$, -SO_2NH_2, -SO_2NHR, -$SO_2N(R)_2$, -SH or -SO_kR.

14. The method of Claim 13 wherein R_7 is a phenyl group; and R_2 is 2-(imidazol-4-yl)ethyl.

15. A method of inhibiting rejection of a transplanted organ, tissue or cell in a mammal, the method comprising the step of administering to the recipient mammal an effective amount of an anti CD40L monoclonal antibody or rapamycin and an effective amount of a compound represented by the following structural formula:

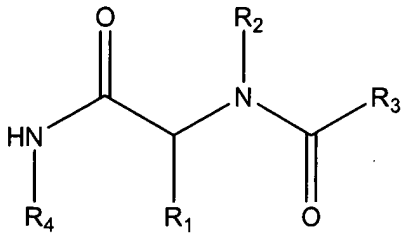


;

or a pharmaceutically acceptable salt of the compound.

16. The method of Claim 15 wherein the transplanted organ, tissue or cell is a transplanted heart, kidney, lung, liver, pancreas, skin or bone marrow.

17. A composition comprising an immunsuppressive agent and a compound represented by the following structural formula:



or a physiological salt thereof, wherein:

R_1 is a substituted or unsubstituted aryl group or a substituted or unsubstituted alkyl group;

R_2 is an optionally substituted aralkyl group or an alkyl group substituted with $-NR_5R_6$;

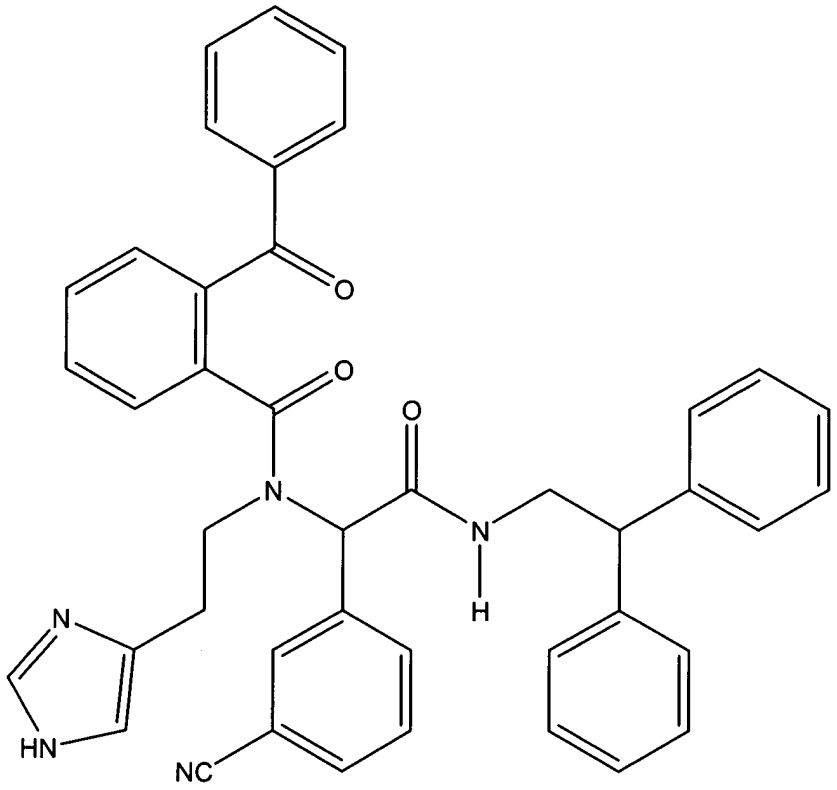
R_3 is a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group;

R_4 a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group; and

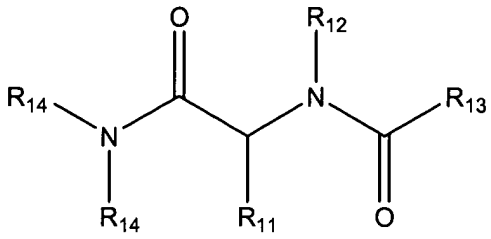
R_5 and R_6 are independently selected from a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group or R_5 and R_6 taken together with the nitrogen to which they are attached are a non-aromatic heterocyclic group.

18. The composition of Claim 17 wherein the immunosuppressive agent is an anti CD40L monoclonal antibody or repamycin.

19. A composition comprising an anti CD40L monoclonal antibody or repamycin and a compound represented by the following structural formula:



or a pharmaceutically acceptable salt of the compound.



R_{11} is -H, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heteroaralkyl;

R_{12} is alkyl substituted with $NR_{15}R_{16}$, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaralkyl, or a substituted or unsubstituted heterocycloalkylalkyl;

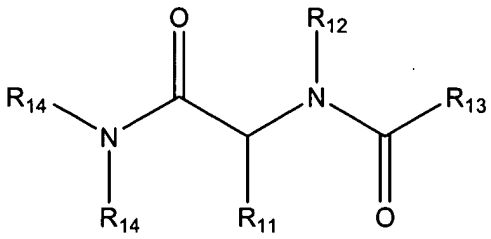
R_{13} is a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted cycloalkylalkyl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted heteroaralkyl, a substituted or unsubstituted benzophenonyl, or a substituted or unsubstituted cycloalkylalkyl; and

each R_{14} is independently, -H, a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, substituted or unsubstituted aralkyl or a substituted or unsubstituted heteroaralkyl;

R_{15} and R_{16} are independently selected from H, a substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted aryl or unsubstituted aralkyl or R_{15} and R_{16} together with the nitrogen to which they are attached are a heterocycloalkyl.

20. A method of inhibiting rejection of a transplanted organ, tissue or cell in a mammal, the method comprising the step of administering to the recipient

mammal an effective amount of an immunosuppressive agent and an effective amount of a compound represented by the following structural formula:



R_{11} is -H, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heteroaralkyl;

R_{12} is alkyl substituted with $NR_{15}R_{16}$, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaralkyl, or a substituted or unsubstituted heterocycloalkylalkyl;

R_{13} is a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted cycloalkylalkyl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted heteroaralkyl, a substituted or unsubstituted benzophenonyl, or a substituted or unsubstituted cycloalkylalkyl; and

each R_{14} is independently, -H, a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, substituted or unsubstituted aralkyl or a substituted or unsubstituted heteroaralkyl;

R_{15} and R_{16} are independently selected from H, a substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted aryl or unsubstituted aralkyl or R_{15} and R_{16} together with the nitrogen to which they are attached are a heterocycloalkyl.